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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,373	07/18/2003	Jennifer L. Whistler	316E-001510US	4987

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EXAMINER	
BRANNOCK, MICHAEL T	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,373	WHISTLER ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-78* is/are pending in the application.

4a) Of the above claim(s) *12,26 and 30-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-25 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *032604,081004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 4/1/2004, have been entered in full.

Claims 12, 26, 30-78 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention there being no allowable generic or linking claim. Applicant's election of Group II, claims 1-11, 13-25, 27-29, as the claims relate to GASP1 and a delta opiate receptor, in applicant's response of 7/25/2006, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore the restriction requirement is deemed proper and made final. However, it is noted that claim 15 was erroneously left out of Group II in the restriction requirement, and is hereby reinstated.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 81 for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13-17, 18-25, 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhancing agonist induced down-regulation of a GPCR by expressing a GASP1 or GASP2 polypeptide, and for inhibiting such down-regulation by expressing a carboxyl terminal peptide there of, *in vitro*, does not reasonably provide enablement for genus of administering an inhibitor or administering a polypeptide that is other than the polypeptide of SEQ ID NO: 2 or 6, nor for *in vivo* uses of the methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification describes experiments showing that a protein, referred to in the art as either KIAA0443, AB007903, or PIPS, now termed GASP1, promotes agonist induced shuttling of the delta opiate receptor from the plasma membrane to the lysosome where it is subsequently degraded – thus resulting in down regulation as measured by radio-ligand binding assays. This down regulation could be inhibited by expressing a 497 amino acid portion of the carboxyl terminus of the GASP1 protein. Conversely, the down regulation could be enhanced by overexpressing the GASP1 protein. The specification surmises that this GASP function could be general to the larger class of GPCRs, which has subsequently been born-out by other researchers, see, Simonin-F. et al., Journal of Neurochemistry 89(766-775)2004. At pages 26 and 75, the specification discusses the possibility that inhibitors or enhancers of the GASP/GPCR interaction could be used therapeutically, either alone or as adjuncts to other drugs so as to heighten the effects of other drugs or make them more specific. These possibilities appear to be art-recognized, see Gray-JA et al, Science 297(529-531)2002 who review Applicant's published

work. Unfortunately however, with the exception of GPAS proteins themselves as discussed above, these inhibiters and enhancers have yet to be discovered.

Claim 1 and 13 requires the use of a genus of compounds that inhibit the specific interaction between a GASP protein and a GPCR. While it is certainly possible that such a genus may one-day be found, the specification has merely provided an invitation to the skilled artisan to try to find such compounds. None are known in the art and none are taught in the specification, with the exception of the truncated GASP1. Claims 1 and 13 require methods of inhibiting the specific binding in the GASP/GPCR interaction, particularly the claims encompass, and claim 13 specifically requires, that the method be practiced *in vivo*. The truncated GASP1 is a large protein and it was used in the method by expressing it *in vitro* in a host cell transfected with a vector encoding it. These are intriguing findings scientifically, but are not sufficient to enable the instant broad claims that encompass every possible means that may eventually be found to practice the invention, e.g. the discovery of drugs and compounds that is contemplated in the specification at pages 26 and 75. The specification provides only a superficial and general discussion of the use of vectors and viruses for *in vivo* delivery of the polypeptides, pgs 42-43, yet no specific teachings are provided to accomplish any particular method *in vivo*.

Claims 18-25, 27-29 require contacting a GPCR with a GASP polypeptide, or variant thereof, so as to effect enhancement of agonist induced down regulation of a GPCR. The only direct teaching of this method in the specification is that achieved with overexpression of the GASP1 polypeptide having the naturally occurring amino acid sequence of SEQ ID NO: 2. It should also be pointed out that Simonin-F. et al. (supra) teach that GASP2 has similar properties,

see col. 1 of pg 767. The claims, as well as those of 1-11 and 13-17, require the use of a vast genus of amino acid sequence variants of the naturally occurring SEQ ID NO: 2 and 6, yet the specification has only provided sufficient guidance to use naturally occurring SEQ ID NO: 2 and 6 for the inhibition or enhancement of agonist induced down regulation of a GPCR.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). Guo-HH et al. PNAS 101(25)9205-9210, 2004, recently reviewed the art and conducted an extensive study on the effect of amino acid substitution on the functionality of a wide variety of proteins and found that on average a single amino acid substitution had a 34% chance inactivating the functionality of the protein, see the Abstract.

However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these

positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 2 or 6 that can be used in the claimed methods.

The claims are, in essence, single means claims, because the claims encompass any composition having the recited activities whereas the instant specification only discloses those two naturally occurring compositions known to the inventor, i.e. SEQ ID NO: 2 and 6. Similarly, the instant claims encompass every mode of administration, e.g. *in vivo* methods, yet the specification discloses only *in vitro* transfection of isolated cells. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). With regard to enablement for artificially constructed variants of the polypeptides encoded by

SEQ ID NO: 2 and 6, the instant fact pattern is actually several steps removed and deficient from that of *Hyatt*. The instant specification does not disclose any working examples of artificially constructed variants of the polypeptides encoded by SEQ ID NO: 2 and 6 nor any *in vivo* use of the methods.

Therefore, due to the large quantity of experimentation necessary to generate the infinite number of variants required by the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity or specific instruction for *in vivo* use, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any particular structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649. Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

October 17, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER